REMARKS/ARGUMENTS

Claims 1, 7 and 9-15 have been limited to the administration of mesna or dimesna. Basis for this amendment is found, for example, on page 6, lines 15-16 and in claim 2 of the application as filed.

Claim 2 has been cancelled herein.

Claims 19-23 are new. These claims correspond to claims 1 and 9-12, respectively, in which the method is limited to the administration of mesna. Basis for this amendment is found for example on page 7, lines 14-17, on page 9, lines 11-18, and in the examples of the application as filed.

Claims 1, 3-5, 7-15 and 19-23 are pending in the present application.

Recordation of Substance of Interview with Examiner Thomas

In accordance with 37 CFR §1.113(b), the Applicants submit the following recordation of the substance of a telephone interview with the Examiner that occurred on September 24, 2009.

Present at the interview were Examiner Thomas and Patricia Folkins (Agent for the Applicants). There were no exhibits shown or demonstrations conducted during the interview. The merits of all of the currently rejected claims were discussed. The specific prior art discussed was Friedman (Amer. J. Kidney Diseases, 2003, 41(2); 442-446), Ventura (Pharmacology, 2003, 68(2):105-114) and Pendyala, et al. Clinical Cancer Research, 2000, 6(4):1314-1321.

During the interview various objections were discussed including the species election and obviousness rejections. With respect to the species election, it was noted that claims 2 and 15 were withdrawn as being directed to a non-elected species however, if the subject matter from any one of these claims were to be reintroduced into independent claims, the Examiner stated that this would shift the species under examination and they would be considered.

With respect to the obviousness rejection, the Agent for the Applicants asked for clarification of the calculations presented in the Office Action and then a discussion about the difference in dosing amounts between the prior art and the current application was discussed. The Examiner agreed that this could represent a basis for arguing that the present invention possesses an unexpected advantage. Various options for amending the claims were discussed. No conclusions were reached.

The Official Action dated June 10, 2009, has been carefully considered. It is believed that the amended claims submitted herewith and the following comments represent a complete response to the rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Elections/Restrictions

The Office Action has expanded the scope of the term "derivatives of mesna" to include N-acetylcysteine (NAC) on the basis that it contains a sulfhydryl group and the implication in the Applicants' previous response that NAC may be used to establish the predictability or unpredictability of the results reported in the present application.

The Applicants strongly disagree with the Office Action's classification of NAC as a derivative of mesna (as explained in greater detail hereinbelow), however, to expedite the allowance of this application, the Applicants have limited the claims to a method comprising the administration of mesna or dimesna.

35 UCS § 112, Second Paragraph

The Office Action rejects claim 1 under 35 UCS § 112, Second Paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the application regards as the invention. Specifically, the Office Action notes that claim 1 recites that mesna is removed from the plasma during dialysis, however for embodiments within the claims where mesna is not administered, such as the administration of a mesna derivative, it is not clear what meaning "removal of mesna" would have. The Office Action further states that it is not clear what compounds are within the scope of "derivatives" of mesna and which are excluded.

Claim 1 has been amended to specify that the derivative of mesna is dimesna and to clearly state that mesna and dimesa are removed from the plasma during dialysis.

In view of the above amendment, the Applicants request that the rejection of claim 1 under 35 UCS § 112, Second Paragraph, be withdrawn.

35 UCS § 112, First Paragraph

Claims 1, 3-5 and 7-14 have been rejected under 35 UCS § 112, First Paragraph, for failing to comply with the Written Description requirement. The Office Action alleges that "derivatives" of mesna have not been disclosed in a manner to provide sufficient written description demonstrating that the Applicant was in possession, at the time of filing, of the genus claim to "derivatives" of mesna, nor have a representative number of such derivative compounds been named or otherwise described.

While not agreeing with the Office's rejection, to expedite the allowance of this application, the Applicants have amended the claims to replace the term "derivatives of mesna" with "dimesna". Dimesna is specifically named as an example of a derivative of mesna, for example, on page 6, lines 15-16, of the application as filed. Therefore the

Applicant submits that there is written description support in the present application as filed for dimesna as the derivative of mesna.

In view of the above amendment, the Applicants request that the rejection of claims 1, 3-5 and 7-14 under 35 UCS § 112, First Paragraph, be withdrawn.

35 UCS § 103(a)

The Office Action has maintained the rejection of claims 1, 3-5 and 7-14 under 35 USC § 103(a) as being obvious over Pendyala, et al. Clinical Cancer Research, 2000, 6(4):1314-1321 (herein after "Pendyala") and Cohen, Molecular and Cellular Biochemistry, 2003, 244(1-2):31-36 (herein after "Cohen"), in view of Wilcox, WO 01/30352 A1, 2001 (hereinafter "Wilcox").

In a previous Office Action dated May 12, 2008, it is stated that Pendyala teaches that mesna can reduce cystine and homocystine to cysteine and homocysteine (Hcy), that cysteine and Hcy levels are inversely related to mesna levels and that these reduced forms are readily cleared by renal excretion. Further, this previous Office Action states that Cohen teaches that Hcy is a substance known to produce vascular damage and accumulates in subjects with uremia, such as those with ESRD and treatments for uremia include dialysis. Finally, this previous Office Action states that Wilcox teaches that high total plasma homocysteine (t-Hcy) concentration is considered a risk factor for atherosclerosis, occlusive vascular disease and coronary artery disease and because folic acid (a known reducer of t-Hcy concentration) is used in the treatment of coronary artery disease resulting from hyperhomocysteinemia, and in arterial and venous occlusive diseases and has been studied in athero- and thrombogenesis, there is an implication that reduction of Hcy levels will reduce the risk of cardiovascular related diseases, such as atherosclerosis and venous thrombosis. This previous Office Action therefore combined the teachings of Pendyala and Cohen with Wilcox to conclude that it would have been obvious to one of skill in the art at the time of the invention to

administer mesna to a subject, including a human, with end-stage renal disease (ESRD) to lower t-Hcy levels and to combine this mesna administration with dialysis treatment, conducted during or after mesna administration.

The Applicants have amended claim 1, and accordingly claims 3-5 and 7-14, dependent thereon to specify that the derivative of mesna is dimesna. New claims 19-23 are restricted to a method comprising the administration of mesna and does not include "derivatives of mesna", the Applicants submit that the claims submitted herewith are patentable over this cited art for the reasons that follow.

The Applicants do not disagree that it is known in the art to reduce plasma t-Hcy levels to reduce the risk of cardiovascular related diseases, such as atherosclerosis and venous thrombosis. As previously argued, the Applicants do not agree that the teachings in Pendyala, which relate to administration of mesna to patients with functioning kidneys, unlike patients with ESRD, in combination with Cohen and Wilcox, render the presently claimed invention obvious. The present application unexpectedly shows for the first time that mesna is able to exchange with the Hcy on Hcy-cys-34 albumin thereby releasing free Hcy (reduced and mixed disulfide forms), which, is eliminated, along with mesna (which is also removed from its bound form in the plasma) by dialysis. Applicants had previously argued that these results are particularly unexpected in view of the fact that a similar strategy was previously attempted using N-acetylcysteine (NAC), however, in patients on chronic hemodialysis, it was not successful (see Friedman, et al., Am. J. Kidney Dis. 2003, 41:442-446). This contrasts with a study on healthy subjects where NAC was able to lower t-Hcy (see Ventura, et al. Pharmacology, 2003, 68:105-114).

The present Office Action argues that the fact that mesna was able to decrease post-dialysis t-Hcy, while it itself is also removed from the plasma during dialysis in patients with ESRD, is not unexpected in view of Friedman and Ventura. In support of this, the

Office Action creates ratio of reduction of t-Hcy in patients with a functioning kidney upon administration of NAC vs a reduction of t-Hcy in patients with a non-functioning kidney upon administration of NAC using the results reported in Ventura and Friedman, respectively, and uses this ratio to extrapolate the results reported in Pendyala for reduction of t-Hcy in patients with a functioning kidney upon administration of mesna to an "expected" reduction in t-Hcy in patients with a non-functioning kidney upon administration of mesna (as reported in the present application). Using the calculated ratio of reduction of t-Hcy by NAC in patients with a functioning kidney vs patients with a non-functioning kidney the Office Action predicts that reduction of t-Hcy using NAC, or a derivative thereof, in patients with a functioning kidney, will be 1.5-1.82 times better than that in a patient with a non-functioning kidney. Based on this number, the Office Action calculates an expected reduction of t-Hcy by mesna (which the Office Action asserts is a derivative of NAC) in patients with a non-functioning kidney, based on the results of Pendyala and an expected 1.5-1.82 times reduction in activity, of 52-66%. The Office Action submits that 52-66% is comparable to the activity reported in the present application and therefore the results of the present application were predictable and obvious. The Applicants submit that the calculations and reasoning reported in the Office Action are flawed for several reason as outlined below.

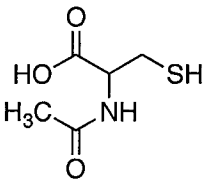
Firstly, it is noted that the Office Action recognizes that the doses of NAC administered to the patients are different in Ventura and in Friedman and therefore deliberately extrapolates the results reported in Ventura to obtain a "projected" t-Hcy reduction for "healthy" patients given the same dosage of NAC per day that was administered to "unhealthy" patients in Friedman (i.e. 2400 mg). Even the Office Action admits that this extrapolation of results is not proper as it "ignores potential saturation behaviour" and the Applicants agree that it is completely wrong to assume that relationships between dose and t-Hcy levels are linear. That there is no linear relationship between t-Hcy levels and dose of Mesna is very clear in the results shown in Figure 2 of Pendyala. Irrespective of this, while the Office Action goes to great lengths to extrapolate the dose

levels reported in Ventura to those reported in Friedman, the Office Action fails to make a similar dose extrapolation for the levels reported in Pendyala to those reported in the present application. Pendyala reports the intravenous administration of Mesna to patients with a functioning kidney under conditions of constant infusion over 36 hours at a dose rate ranging from 2 g/m^2/day to 8 g/m^2/day, with 7 g/m^2/day being optimum. This dose amount corresponds to the administration of 3.46 grams/day to 13.84 grams/day or 5.29 *grams* to 20.76 *grams* over the entire treatment protocol (36 hours). In the study reported in the present application, patients with non-functioning kidneys were given only 5 *milligrams* per kg or, assuming an average weight of about 70 kg, about 350 *milligrams* of mesna in *a single intravenous dose*. Therefore the study reported in the present application administered from about 94% to about 98% less mesna to the patients than the study of Pendyala. This factor was not considered in the analysis reported in the Office Action.

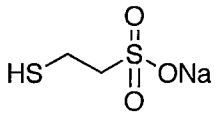
Secondly, as noted above, it is improper to assume that the relationship between dose and activity is linear. This is particularly the case where the drug is administered under completely different conditions. In Pendyala, mesna is administered to patients with functioning kidneys by continuous infusion over 36 hours in combination with a co-infusion of ifosamide (24 hour infusion). In the study in the present application, mesna is administered to patients with non-functioning kidneys alone as a single intravenous intra-dialytic dose of about 350 mg. The Applicant submits that, even if the dose-response were linear, the 29% reduction in plasma t-Hcy reduction compared to control that is reported in the present application for the administration of only 350 mg of mesna, on its own, to patients with non-functioning kidneys, would have been completely unexpected to a person skilled in the art based on the teaching in Pendyala, alone or in combination with Friedman and Ventura.

A third reason that the calculations and reasoning reported in the Office Action are flawed is the assumption that NAC is a derivative of mesna. This assumption is used as

the justification for extending the results of Friedman and Ventura to Pendyala and the present application. That NAC is a derivative of mesna is scientifically and chemically inaccurate. The structure of mesna and NAC are shown below.

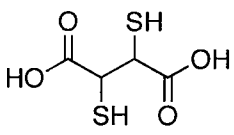


N-acetylcysteine (NAC)



Mesna

It can be seen that the only similarity between mesna and NAC is the thiol group that they each contain. The basic backbone structure of NAC is that of the amino acid cysteine with an acetyl functional group. Mesna does not have an amino acid-like structure, i.e. it does not contain an amine or a carboxylic acid functional group. It is important to note that just because an agent has a thiol group does not mean it will be effective in lowering plasma t-Hcy. The Applicants supported this argument in their response dated February 23, 2009 using NAC as an example of a thiol containing molecule that has been previously reported to not lower t-HCY levels in patients with non-functioning kidneys (Friedman). Another example of a thiol-containing agent which fails to lower plasma total homocysteine levels in dialysis patients is dimercaptosuccinic acid (DMSA – structure shown below) as reported in House et al. American Journal of Kidney Diseases (2004) 44(4):689-694. DMSA also failed to displace homocysteine from plasma protein *in vitro* as reported in Urquhart et al. Journal of Pharmaceutical Sciences (2006) 95(8):1742-1750. Copies of the latter two papers have been provided in a supplementary Information Disclosure Statement submitted concurrently herewith.



Dimercaptosuccinic acid (DMSA)

The Applicants have cited NAC and DMSA as examples of thiol containing compounds, not as examples of derivatives of mesna, but to support the argument that not all thiols are alike in their ability to participate in a thiol exchange reaction with the Hcy bound to cys^{34} on albumin, thereby liberating free Hcy into the plasma for elimination from the body. The Applicants had no intention for NAC (or DMSA) to be included within the scope of claim 1 as a derivative of mesna, which is clear from the fact that they used NAC, and now DMSA, to show that mesna is very different from these compounds in its ability to lower tHcy in the plasma of patients with ESRD.

A fourth reason that the calculations and reasoning reported in the Office Action are flawed is that the Office Action fails to consider that the studies reported in Pendyala never administered mesna on its own, but always with ifosfamide. Pendyala actually teaches that the "individual effects of ifosfamide and mesna on plasma thiol modulation are unclear, and this relationship could be clarified by a randomized cross-over trial comparing the effects of a continuous infusion of mesna versus ifosfamide/mesna on thiol levels" (page 1320, column 1, lines 7-11, of Pendyala). Pendyala merely presents *in vitro* data showing that mesna can reduce homocystine to homocysteine. Therefore there is no direct evidence in Pendyala that mesna, on its own, reduces homocystine *in vivo* to homocysteine which is then cleared by renal excretion. Pendyala admits that this conclusion cannot be made given the potentially confounding effect of co-administration of ifosfamide. It should be noted that Pendyala's results show that the reduction in plasma t-Hcy maxed out at 24 hours when ifosfamide administration stopped and then actually started to increase (at 28 hours) even while mesna was still being delivered (see Figure 2 of Pendyala). This clearly raises significant doubt that mesna was acting alone to lower plasma t-Hcy.

Therefore, the Applicants submit that the results reported in the present application, for example in Figure 2 where there was a 29% greater reduction in plasma t-Hcy post-

dialysis after administration of only 5 mg/kg of mesna compared to control, is in no way comparable to or predictable from the results reported in the prior art. To summarize, this is because (a) the results reported in Friedman and Ventura cannot be used to predict the activity of mesna in patients with a non-functioning kidney because both Friedman and Ventura used NAC, a completely different compound from mesna used and claimed in the present application; (b) extrapolation of dose-response results to different doses assuming a linear relationship is improper; and (c) the results reported in Pendyala cannot be used to predict the activity of mesna in patients with a non-functioning kidney because (i) the patient group in Pendyala had functioning kidneys, (ii) Pendyala administered 94% to 95% more mesna than was administered in the present study, (iii) administration in Pendyala was by continuous infusion over 36 hours where the present study used a single intravenous injection, and (iv) Pendyala co-administered mesna with ifosamide whereas the present study administers mesna on its own.

With respect to removal of mesna by dialysis, the Office Action argues that one of ordinary skill in the art would expect the removal of at least some of the mesna by this route. Again the Office Action supports this conclusion using the results for NAC. As argued above, it is improper to use NAC as a predictive tool for mesna as NAC is not a derivative of mesna, is structurally very different from mesna and therefore the results for one of these molecules cannot be used to predict results for the other. The Office Action cites In re Best (1995 USPQ 430) and In re Fitzgerald (205 USPQ 594) to support the argument that, in the situation where "the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed[,] the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not posses the characteristics relied on"." The Applicant submits that the Office Action's assumption that the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed is improper. It appears that the Office Action's conclusion about mesna's clearance by dialysis is based on the

results for NAC, which as argued above, is no way "identical to a product instantly claims" or "inherently includes functions that are newly cited". It remains that, as of the filing date of the present application, it was not known whether or not mesna could be removed from the body by dialysis. This, coupled with the unexpected reduction in t-Hcy levels in the plasma of patients with non-functioning kidneys, post dialysis, renders the method claimed in the present application non-obvious over the cited art.

The Applicants submit that the above analysis applies to the administration of mesna to ESRD patients as well as dimesna as presently claimed for the reasons that follow. Dimesna is the oxidized form of mesna. There are several tissues that are capable of reducing dimesna to mesna as reported in Verschraagen et al. (2004) Biochemical Pharmacology 68:493-502 (copy provided in the Supplemental Information Disclosure Statement filed concurrently herewith). Verschraagen show intestine cytosol can reduce dimesna to mesna. The Applicants submit that dimesna administered by oral delivery in the method of the present application is reduced in the intestine and absorbed as mesna into the circulation. The Applicants note, in particular, the concluding paragraph (page 501) of Verschraagen, where it is stated that "[t]he use of BNP7787 [dimesna] as an oral drug might be limited because of the high BNP7787 reductive activity of the small intestine cytosol. Intestinal absorption of BNP7787 might lead to high concentrations of mesna in the circulation that could inactivate cisplatin." In the context of the present work, the intestine can be viewed as an organ that will reduced dimesna (BNP7787) into mesna and yield a high concentration of mesna in the blood which would then be available to decrease plasma t-Hcy. Accordingly, the Applicant submits that the present invention includes both mesna and dimesna.

The Supreme Court in *KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. 398, 2007), quoting *In re Kahn,* 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational

underpinning to support the legal conclusion of obviousness." For the reasons provided above, the Applicants submit that there is no rational underpinning to the conclusion of obviousness provided in the present Office Action. Accordingly, the Applicants submit, that the present invention was in no way predicted based on the teachings of the cited art and the Office Action has not established a *prima facie* case of obviousness for the subject matter of claims 1, 3-5 and 7-14.

In view of the above amendments and arguments the Applicants request that the Examiner's rejection of claims 1, 3-5 and 7-14 under 35 USC 103(a) be withdrawn.

Claims 9-12 have been rejected under 35 UCS § 103(a) as obvious over Friedman as applied to claims 1, 3-5, 7-8 and 13-14 above.

The Office Action notes that Friedman does not teach a weekly dose within the ranges of claims 9-12 however the Office Action submits that it would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the dose and timing of the dosing with respect to when dialysis is conducted to give amounts within the instant claimed weekly and three times weekly amounts. The Office Action refers to this as "routine optimization".

Claim 1, and accordingly claims 9-12 dependent thereon, have been amended to be limited to the administration of mesna or dimesna. Friedman only teaches the administration of NAC and, as noted above, teaches that NAC does not have a statistically significant t-Hcy-lowering effect. As argued above, NAC would not be considered by a person skilled in the art to be a derivative of mesna therefore the Applicants submit that, other than showing that not all thiols are effective in reducing t-Hcy in ESRD patients, the results for NAC have no bearing on the claims of the present application. Even if the results for NAC were relevant, it would not have been "routine optimization" for a person skilled in the art to lower the dose from the 16.8 *grams* per

week used by Friedman (which provided no significant results) to the 1.0-25 mg/kg, or assuming an average weight of 70 kg, 0.070 grams to 1.75 grams per week that is claimed in claims 9-12. If any optimization were to be done, then a person skilled in the art, seeing the non-significant effect of NAC on t-Hcy levels in dialysis patients, would have been lead to using higher doses, i.e. they would have been lead away from the doses that claimed.

In view of the above amendments and arguments the Applicants request that the Examiner's rejection of claims 9-12 under 35 USC 103(a) be withdrawn.

35 UCS § 102/103

Claims 1, 3-5, 7-8 and 13-14 have been rejected under 35 UCS § 102(a) as anticipated by, or, in the alternative, under 35 UCS § 103(a) as obvious over Friedman (Amer. J. Kidney Diseases, 2003, 41(2); 442-446). For this rejection the Office Action assumed that the intention of previous claim 1 was the removal of mesna or the derivative of mesna from the plasma during dialysis. The Applicants agree with this interpretation and have amended claim 1 herein to correct this inadvertent error.

Friedman teaches the administration of NAC to patients undergoing hemodialysis and the Office Action alleges that it teaches an average 19.2% reduction in t-Hcy in all patients receiving NAC. Further, the Office Action equates NAC to a "derivative of mesna". The Applicants note that the 19.2% reduction in t-Hcy for the NAC group was not significantly different from the control group, therefore it is not scientifically correct to attribute this reduction in t-Hcy to NAC administration. Throughout Friedman it is taught that NAC did not have a statistically significant t-Hcy-lowering effect (see the abstract; page 444, column 2, lines 18-20; page 445, column 2, lines 6-8; and page 446, column 1, lines 1-3, of Friedman). This conclusion is drawn by Friedman, despite the fact that the patients received 2400 mg per day for 4 weeks! Friedman also reports that two previous preliminary studies of dialysis patients had not found that dialysis dramatically

reduces t-Hcy levels after NAC therapy (page 445, column 2, 5th paragraph of Friedman). Accordingly, the Applicants strongly disagree with the Examiner's conclusion that Friedman would lead a person skilled in the art to conclude that NAC has activity in reduction of t-Hcy. Further, as argued above, NAC would not be considered by a person skilled in the art to be a derivative of mesna therefore the Applicants submit that, other than showing that not all thiols are effective in reducing t-Hcy in ESRD patients, the results for NAC have no bearing on the claims of the present application.

As the Office Action equates NAC to "derivative of mesna", it concludes that Friedman anticipates any claim that involves administering an effective amount of a mesna derivative to lower plasma t-Hcy levels in a subject having ESRD. While the Applicants disagree that NAC is a derivative of mesna and that Friedman teaches that NAC lowers plasma t-Hcy levels in a subject having ESRD, to expedite the allowance of this application, they have amended claim 1, and accordingly and claims 3-5, 7-8 and 13-14, dependent thereon to specify that the derivative of mesna is dimesna. As these claims now only cover the administration of mesna or dimesna, and NAC is not related to mesna or dimesna, the Applicant submits that they are not anticipated or obvious over Friedman.

In view of the above amendment and argument, the Applicants request that the rejection of claims 1, 3-5. 7-8 and 713-14 under 35 UCS § 102(a) or 103(a), be withdrawn.

In view of the foregoing, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, he is kindly requested to contact Patricia Folkins by telephone at 416-957-1683 at his convenience.

The Commissioner is hereby authorized to charge any deficiency in fees or credit any overpayment to our Deposit Account No. 02-2095.

Respectfully submitted,

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